

production medium and feeding the eukaryotic cells using an enriched media having 5-methylthioadenosine during a time period. In one aspect of this embodiment, the enriched media can have at least about 1 nM 5-methylthioadenosine. In one aspect of this embodiment, the cell culture production medium can comprise one or more acids selected from lactic acid, phenyl lactic acid, indolelactic acid, succinic acid, alpha-hydroxyisovaleric acid, alpha-hydroxyisocaproic acid, 2-(4-hydroxy-phenyl)lactic acid, or 2-hydroxy-3-methylvaleric acid, salts of these acids, esters of these acids and combinations thereof. In one aspect of this embodiment, the cell culture production medium can comprise sugars, amino acids, vitamins, salts, trace metal ions, purines, and/or pyrimidines. In one aspect of this embodiment, the cell culture production medium can comprise salts or esters of 5-methylthioadenosine. In one aspect of this embodiment, the cell culture production medium can have a pH of about 6.5 to about 8. In one aspect of this embodiment, the cell culture production medium does not have a protein derived from an animal. In one aspect of this embodiment, the cell culture production medium can be a serum-free medium. In one aspect of this embodiment, the cell culture production medium can be a chemically-defined medium. In one aspect of this embodiment, the eukaryotic cells can be selected from Baby Hamster Kidney cell lines, Chinese Hamster Ovary cell lines, Murine myeloma cell lines, Mouse myeloma cell lines, Human embryonic kidney cell lines, Human-retina-derived cell lines, and/or Amniocyte cell lines. In one aspect of this embodiment, the protein can be selected from the group consisting of an antibody or a fragment or derivative thereof, a fusion protein, and a physiologically active non-antibody protein. In one aspect of this embodiment, the method can produce a titer of a protein at least about 2% greater than a titer of a protein in a cell culture production medium not having at least about 10 nM 5-methylthioadenosine. In one aspect of this embodiment, the enriched media can optionally comprise nicotinamide. In one aspect of this embodiment, the method of producing a protein can be a fed-batch method.

[0011] In one exemplary embodiment, the method of producing a protein can comprise culturing eukaryotic cells having a nucleic acid encoding the protein in a cell culture production medium and feeding the eukaryotic cells using an enriched media having nicotinamide during a certain time period. In one aspect of this embodiment, the enriched media can have at least about 5 nM nicotinamide. In one aspect of this embodiment, the cell culture production medium can comprise one or more acids selected from lactic acid, phenyl lactic acid, indolelactic acid, succinic acid, alpha-hydroxyisovaleric acid, alpha-hydroxyisocaproic acid, 2-(4-hydroxy-phenyl)lactic acid, or 2-hydroxy-3-methylvaleric acid, salts of these acids, esters of these acids and combinations thereof. In one aspect of this embodiment, the cell culture production medium can comprise sugars, amino acids, vitamins, salts, trace metal ions, purines, and/or pyrimidines. In one aspect of this embodiment, the cell culture production medium can comprise salts or esters of nicotinamide. In one aspect of this embodiment, the cell culture production medium can have a pH of about 6.5 to about 8. In one aspect of this embodiment, the cell culture production medium does not have a protein derived from an animal. In one aspect of this embodiment, the cell culture production medium can be a serum-free medium. In one aspect of this embodiment, the cell culture production

medium can be a chemically-defined medium. In one aspect of this embodiment, the eukaryotic cells can be selected from Baby Hamster Kidney cell lines, Chinese Hamster Ovary cell lines, Murine myeloma cell lines, Mouse myeloma cell lines, Human embryonic kidney cell lines, Human-retina-derived cell lines, and/or Amniocyte cell lines. In one aspect of this embodiment, the protein can be selected from the group consisting of an antibody or a fragment or derivative thereof, a fusion protein, and a physiologically active non-antibody protein. In one aspect of this embodiment, the method can produce a titer of a protein at least about 2% greater than a titer of a protein in a cell culture production medium not having at least about 50 nM nicotinamide. In one aspect of this embodiment, the enriched media can optionally comprise 5-methylthioadenosine. In one aspect of this embodiment, the method of producing a protein can be a fed-batch method.

[0012] The disclosure, at least in part, provides a method for increasing production of a protein.

[0013] In one exemplary embodiment, the method for increasing production of a protein can comprise culturing eukaryotic cells in a cell culture medium, supplementing the cell culture medium with 5-methylthioadenosine, and expressing a protein. In one aspect of this embodiment, concentration of 5-methylthioadenosine can be at least about 10 nM. In one aspect of this embodiment, concentration of 5-methylthioadenosine can be about 10 nM to about 200 nM. In one aspect of this embodiment, the cell culture medium can comprise one or more acids selected from lactic acid, phenyl lactic acid, indolelactic acid, succinic acid, alpha-hydroxyisovaleric acid, alpha-hydroxyisocaproic acid, 2-(4-hydroxyphenyl)lactic acid, or 2-hydroxy-3-methylvaleric acid, salts of these acids, esters of these acids and combinations thereof. In one aspect of this embodiment, the cell culture medium can comprise sugars, amino acids, vitamins, salts, trace metal ions, purines, and/or pyrimidines. In one aspect of this embodiment, the cell culture medium can comprise salts or esters of 5-methylthioadenosine. In one aspect of this embodiment, the cell culture medium can have a pH of about 6.5 to about 8. In one aspect of this embodiment, the cell culture medium does not have a protein derived from an animal. In one aspect of this embodiment, the cell culture medium can be a serum-free medium. In one aspect of this embodiment, the cell culture medium can be a chemically-defined medium. In one aspect of this embodiment, eukaryotic cells can be selected from Baby Hamster Kidney cell lines, Chinese Hamster Ovary cell lines, Murine myeloma cell lines, Mouse myeloma cell lines, Human embryonic kidney cell lines, Human-retina-derived cell lines, and/or Amniocyte cell lines. In one aspect of this embodiment, the protein can be selected from the group consisting of an antibody or a fragment or derivative thereof, a fusion protein, and a physiologically active non-antibody protein. In one aspect of this embodiment, the supplementation with 5-methylthioadenosine increases titer of the recombinant protein by at least about 2%. In one aspect of this embodiment, the cell culture medium can be optionally supplemented with nicotinamide.

[0014] In one exemplary embodiment, the method for increasing production of a protein can comprise culturing eukaryotic cells in a cell culture medium, supplementing the cell culture medium with nicotinamide, and expressing a protein. In one aspect of this embodiment, concentration of nicotinamide can be at least about 50 nM. In one aspect of